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Low Dose Heparin: Bleeding and Wound Complications in the Surgical Patient

A Prospective Randomized Study

H. LEON PACHTER, M.D., THOMAS S. RILES, M.D.

From the Department of Surgery, New York University Medical Center, New York, New York

A randomized prospective study of low dose heparin was performed in 175 surgical patients to determine the frequency of bleeding and wound complications. The patients were divided into three groups: (1) low dose heparin (5000 units two hours before operation and 5000 units every 12 hours following operation for five days); (2) low dose heparin postoperatively only; and (3) a control group. The frequency of bleeding and wound complications was 27% in group I, 7.5% in group II, and 1.4% in group III. The difference between the control patients and those heparinized pre- and postoperatively is statistically significant ($p < 0.005$). None of the patients in any of the three groups had a pulmonary embolus, but the number of patients involved is too small to assess the significance of this finding. However, a bleeding and wound complication rate of 27% is significant. These findings indicate that perhaps the routine use of low dose heparin should be reserved for those patients with preoperative factors indicating an increased risk from thromboembolism.

THE RELATIONSHIP of deep vein thrombosis and the subsequent embolization of thrombus to the pulmonary vasculature was first recognized by Virchow in 1846. With the developments of general anesthesia, and a rapid increase in the variety and frequency of operative procedures, it soon was recognized that postoperative patients were particularly vulnerable to thromboembolis disease. Although the morbidity and mortality from deep vein thrombosis and pulmonary embolism is relatively low, the unpredictable and occasionally catastrophic occurrence of a pulmonary embolus in an otherwise routine postoperative course is often sobering to the surgeon. The observation that pulmonary emboli occurred in patients with no clinical signs of deep vein thrombosis made clear that successful treatment of thromboembolic disease would depend on finding an effective means of prophylaxis.

Encouraged by the enthusiastic reports of Kakkar,[14,16] we initiated the use of low dose heparin for selected operative patients at New York University Medical Center. Among the initial patients receiving low dose heparin, several had significant bleeding problems and two suffered major pulmonary emboli while on low dose heparin. To investigate the problem of bleeding and wound complications, a prospective randomized study was initiated on the general surgical services.

Patients and Methods

One hundred and seventy-five patients (Table 1) undergoing a variety of general surgical procedures, were randomly selected into three groups by chart numbers. The control group consisted of 69 patients. Forty patients received 5000 units of heparin subcutaneously postoperatively every 12 hours for five days. Sixty-six patients received 5000 units of heparin subcutaneously two hours before surgery and every 12 hours postoperatively for five days. Excluded from the study were patients with heparin sensitivity, coagulation disorders,

Reprint requests: Leon H. Pachter, M.D., Department of Surgery, New York University Medical Center, New York, New York 10016.

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TABLE 1. *Types of Operations Performed*

Low Dose Heparin	Pre and Postop Heparin	Control	Postop Heparin Only
Colon resection	5	9	1
Abdominal perineal	2	2	1
Colostomy closure	2	2	0
Diverting colostomy	0	1	0
Gastrectomy	4	8	3
Biliary tract	9	10	8
Hernia	32	22	22
Mastectomy	3	1	1
S and L of varicose veins	1	2	1
Transmetatarsal amputation	3	1	2
Below the knee amputation	1	1	1
I and D abscess of thigh	1	0	0
Excision of large leg lipoma	1	0	0
Excision of tumor of abdominal wall	2	0	0
Hemorrhoids	0	2	0
Meso caval shunt	0	1	0
Fistula-in-ano	0	2	0
Pancreaticojejunostomy	0	1	0
Pheochromocytoma	0	1	0
Intussusception of small bowel	0	1	0
Lumbar sympathectomy	0	1	0
Lap for pancreatic Ca	0	1	0
Total	66	69	40

bleeding ulcers, patients in whom full anticoagulation was indicated and patients undergoing vascular surgery. Patients were examined for clinical signs of deep vein thrombosis and pulmonary embolus throughout the postoperative period.

Results

None of the 175 patients (Table 2) in the study had any clinical evidence of deep vein thrombosis or pulmonary embolus. Of the 66 patients receiving heparin 15 patients developed wound hematomas* including one patient with significant bleeding beneath the flap of a radical mastectomy. Three patients developed gross hematuria. In these last four patients heparin was immediately discontinued. In all, there were 18 bleeding complications for a total of 27%. In the postoperative heparin group of 40 patients two patients developed wound hematomas with subsequent infection and one patient developed gross hematuria, for a bleeding complication rate of 7.5%. In the control group of 69 patients there was only one wound hematoma for a bleeding complication rate of 1.4%. The difference in the bleeding complication rate between the control and heparinized group was statistically significant ($p < 0.005$).

* These required local drainage which was accomplished in the treatment room.

Discussion

Numerous studies have been conducted on either mechanical measures[4,6,7,12,20] to prevent venous stasis or using various anticoagulation regimens to reduce thrombosis.[1,8,10,14,15,16,25]

Sharnoff[21] first reported a decrease in thromboembolic disease in high risk patients using low dose heparin, beginning a few hours before surgery and continuing into the postoperative period. Following this report, no less than ten independent groups of investigators have conducted randomized studies on surgical patients to test the effect of perioperative heparin on deep vein thrombosis and pulmonary embolism. All,

TABLE 2. *Operative Procedures and Complications*

Operation	No. of Patients	Complications	
Heparin Group–66 Patients			
Inguinal hernia	7	Wound hematoma	
Inguinal hernia	1	Hematuria	
Left colon resection	1	Hematuria	
Excision of abdominal wall tumor	1	Hematuria	
Radical mastectomy	1	Bleeding under flaps	
Biliary tract disease	4	Wound hematoma	
Right below knee amputation	1	Wound hematoma	
Colocolostomy	1	Wound hematoma	
Stripping and ligation	1	Wound hematoma	
		Complication rate:	27%
		Pulmonary embolism	0%
Control Group–69 Patients			
Left inguinal hernia	1	Wound hematoma	
		Complication rate:	1.4%
		Pulmonary embolism	0 %
Postop Heparin Only–40 Patients			
Gastrectomy	1	Wound hematoma and infection	
Right inguinal hernia	1	Wound hematoma and infection	
Abd. perineal resection	1	Gross hematuria	
		Complication rate:	7.5%
		Pulmonary embolism	0 %

TABLE 3. *Incidence of Bleeding Complications*

	No Heparin	Low Dose Heparin
Pachter–Riles	1.4%	27%
String–Barcia	0.7%	14%
Gordon–Smith	0.0%	10%
Nicolaides	0.0%	4%
Kakkar	11.7%	16.6%
Gruber	0%	13.7%
Gallus	0%	0%
Lahnborg	0%	0%
Abernethy	0%	0%
Ribaudo	2.6%	2.6%
Stand	0%	0%
Covey	0%	1.7%

TABLE 4. *Low Dose Heparin Studies*

	Patients		
	Control	Low Dose Heparin	Total
Nicolaides 1972	122	122	244
Gordon–Smith 1972	50	100	150
Gallus 1973	118	108	226
Lahnborg 1974	54	58	112
Abernethy 1974	62	63	125
Ribaudo 1975	75	75	150
Strand 1975	50	50	100
Covey 1975	52	53	105
Kakkar 1975	2076	2045	4121
Pachter–Riles 1976	69	66	135
Total	2728	2740	5468

with the exception of two studies,[1,5] have demonstrated a reduction in deep vein thrombosis with the use of low dose heparin. No study to date including Kakkar's[16] is large enough to demonstrate a difference in the mortality between the treated and control groups.* Most authors, however, have felt that the complications incurred from the use of low dose heparin were justified by the reduction in thromboembolic disease.

Earlier reports by Kakkar[14,16] and others has shown that low dose heparin will decrease the postoperative incidence of deep vein thrombosis and pulmonary emboli. More recently reports by String, Barcia[24] and Gruber[11] have emphasized bleeding complications which may occur with the use of heparin in the perioperative period (Table 3). To demonstrate the role of low dose heparin for a given patient one must ask: does the prophylaxis justify the complication? To make this determination, three questions must be answered: 1) What is the incidence of deep vein thrombosis with and without low dose heparin? 2) What is the morbidity and mortality of pulmonary embolism with or without low dose heparin? 3) What are the potential complications from prophylactic perioperative low dose heparin? The incidence of thromboembolic disease is sufficiently low that the observation of thousands of surgical patients are necessary to draw meaningful conclusions from clinical therapeutic trials. Over the past five years a number of studies have been conducted using prophylactic low dose heparin. In an attempt to answer these questions, we have analyzed the collective experience of all these investigators.

In each of the ten studies selected for this discussion, patients were randomized into two groups. The control group received no heparin, the treated group received 5000 units of heparin subcutaneously two hours preoperatively and then every 12 hours thereafter for five to seven days.† In the study by Gallus[8] and Kakkar[16] heparin was given postoperatively every eight hours. The number of patients in each study is given on Table 4.

What is the Incidence of Deep Vein Thrombosis With and Without Low Dose Heparin?

The incidence of deep vein thrombosis (DVT) varies widely in published series depending on the method of detecting the disease. Methods commonly used are: clinical signs and symptoms, venography, and ^{125}I-fibrinogen scanning technique. Each has its disadvantages.

Although often subjective and inaccurate most authors report an incidence of clinical deep vein thrombosis between 0.6–4%.[1,5,16,19,23]

The ^{125}I-fibrinogen scanning technique is noninvasive and highly sensitive for detecting deep vein thrombosis.‡ This technique was used in most series

* Special report—prevention of venous thromboembolism in surgical patients by low dose heparin. Circulation, 55, 2:423A, February, 1977.

† Our study consisted of three groups which included in one group the use of postoperative heparin alone.

‡ Ribaudo et al., however, used 99m technesium microaggregated albumin.

TABLE 5. *Incidence of DVT in Postoperative Control Patients*

Study	Scan Diagnosis (%)	Clinical Diagnosis
Nicolaides	24	—
Gordon–Smith	42	—
Gallus	16	—
Lahnborg	20	—
Abernethy	4.8	1*
Ribaudo	53	4
Strand	20	3*
Covey	9.6	2*
Kakkar	24.6	4

* One cannot determine if these patients were in the control or treated group.

TABLE 6. *Incidence of ^{125}I-fibrinogen Scans Positive for DVT*

Study	Control (%)	Low Dose Heparin (%)
Nicolaides	24	0.8
Gordon–Smith	42	11.0
Gallus	16	1.9
Lahnborg	20	5.0
Abernethy	4.8	6.0
Ribaudo*	53	32.0
Strand	20	6.0
Covey	9.6	7.5
Kakkar	24.6	7.7

* Used 99^{m} Technetium macroaggregated albumin.

and is the basis for most of the data concerning low dose heparin. The problem has been in standardizing the technique and interpreting the results. Table 5 shows that the incidence of DVT in the control patients, as detected by scanning varied from 4.8–53%. Although one would expect a high incidence in the diagnosis of DVT with the scanning technique, the marked disparity between clinical thrombosis and scan interpretations and the variance of investigators in diagnosing DVT questions the meaning of a positive scan.

Most of the enthusiasm for low dose heparin has been based on studies showing a reduced incidence of positive ^{125}I-fibrinogen scans with its use in the perioperative period (Table 6). All except Abernathy[1] and Covey[5] found a significant reduction of positive scans with low dose heparin. Only two authors discussed the effect of low dose heparin on clinical thrombosis. Kakkar[16] noted a reduced incidence from 4% in the control group to 1.9% in the treated group. Ribaudo,[19] on the other hand, found no change: 4% had clinical thrombosis in each group.

In summary, the incidence of DVT in the postoperative surgical patient is probably 4% for clinically apparent cases and 5–50% using scanning techniques, depending on the investigator. Low dose heparin appears to have a remarkable effect on reducing the number of positive scans and will probably reduce the incidence of clinical thrombosis by one-half.[16]

What is the Morbidity and Mortality of Pulmonary Embolism in Surgical Patients With and Without Low Dose Heparin?

Similar to the problem of DVT, the incidence of postoperative pulmonary embolism in control patients varies greatly from one investigator to another, depending on the criteria for making the diagnosis. Some have reported only cases with typical clinical findings; others have relied on angiograms, lung scans or autopsy reports. Depending on the method, the incidence has varied from 0% to 44% (Table 7).

Caution should be taken when relying on lung scanning technique to establish the diagnosis of pulmonary embolus, particularly when doing routine scanning on asymptomatic patients. A number of pulmonary conditions as atelectasis and chronic obstructive lung disease can give an abnormal scan, indistinguishable from a pulmonary embolus.[2] In a well controlled study by Gilday, Poulose and Deland,[9] 121 patients clinically suspected of having pulmonary embolism were studied with both lung scans and pulmonary angiograms. Fifty-three per cent were found to have scans interpreted as "highly probable for pulmonary embolus." Of these, diagnosis could be confirmed by angiography in only 77% of the cases. While a normal lung scan is helpful to the clinician in excluding the diagnosis of pulmonary embolism an abnormal lung scan must be correlated with the clinical findings and other studies.

Counting only the clinical significant cases in all series, the incidence of pulmonary embolism in the control patients during the postoperative period is the same as that reported by Kakkar,[16] 1.2%. In the patients receiving low dose heparin, this was reduced to 0.4% in both Kakkar's study and in the combined randomized studies.[5,8,10,11,17–19,23]

The mortality from pulmonary embolism in surgical patients has been studied by a number of authors. An excellent review of these studies was prepared by Hume.[13] Kakkar[16] estimated 0.5% in designing his cooperative study and reported 16 deaths from pulmonary embolism in 2,076 control patients for an incident of 0.8%.

In his group of 2,045 patients receiving low dose heparin, Kakkar[16] reported only two deaths attributed to pulmonary embolism reducing the incidence to 0.1%. Interestingly, in the 1,347 patients in all of the low dose heparin studies excluding that of Kakkar[16] there

TABLE 7. *Incidence of Pulmonary Embolism*

Study	Control (%)	Low Dose Heparin (%)
Nicolaides	0	0
Gordon–Smith	0	2.0
Gallus	1.0*	0
Lahnborg	?† (44)	? (16)
Abernethy	0 (19)	0 (0)
Ribaudo	2.7 (5.3)	0 (0)
Strand	0	0
Covey	2	0
Kakkar	1.2	0.4
Pachter–Riles	0	0

Parenthesis = diagnosis made by lung scan.

* This study included nonsurgical patients in addition to 226 surgical patients. The author does not state whether the two patients with pulmonary emboli were surgical or medical.

† A total of four per cent had clinical evidence of pulmonary embolism. One cannot determine if these were in the control or treated group.

were no deaths attributed to pulmonary emboli in either the treated or control groups. It should be noted that the overall mortality rate in Kakkar's[16] cooperative study was a remarkably high 4.4% nearly three times that of all the other heparin studies combined. Furthermore of the 180 deaths reported by Kakkar, 100 in the control group and 80 in the treated group, the cause of death was given only in autopsied cases leaving 28% of deaths unexplained in the controls and 34% in the heparinized group.

What are the Potential Complications with Prophylactic Low Dose Heparin?

Prophylactic low dose heparin reduces DVT and postoperative pulmonary embolism. The use of low dose heparin, however, can only be justified if there is an acceptably low complication rate. While some authors have stated that they experienced no bleeding problems[1,5,14,18,20] in patients receiving low dose heparin others have found this bleeding to be significant.[11,24]

In our study we found a remarkably high level of bleeding and wound complication (27%). Three of our cases were complicated by wound infections, but no reoperations were required. Others have had to return patients to the operating room to control bleeding.[10,11,18] String and Barcia,[24] and Gruber[11] raise concern over a 13.7–14% incidence of bleeding. In Kakkar's study[16] there was a 16.6% complication rate in the heparinized patients which included an 8.9% incidence of excessive blood loss in the operating room and a 7.7% incidence of wound hematomas.

Inasmuch as bleeding complications may be as high 10–27% it seems unwarranted to treat all general surgical patients over the age of 40 with prophylactic low dose heparin.

Skinner and Salzman[22] established criteria for selecting patients at risk for pulmonary embolism. In their study, obesity, anticipated bed rest for more than three days, visceral malignancies, surgical dissection in the pelvis and a history of thromboembolic disease or varicose veins were indications for treating their patients with therapeutic doses of Wafarin. In a group of 80 patients with one of the above indications, but with a contraindication to anticoagulation therapy, the incidence of pulmonary embolism was 10%. In their treated group the rate was lowered to 1.7%, but with an 8.6% incidence of postoperative bleeding which included three deaths related to the bleeding. Some of their complications were no doubt secondary to maintaining safe therapeutic levels of anticoagulation. It would seem reasonable that low dose heparin be reserved for the group of patients considered by Skinner and Salzman[22] to be high risk. With an expected rate of pulmonary embolism of 10% in high risk patients, the bleeding rate with low dose heparin can be justified. The goal would be to achieve the same protection offered to this group of patients with Warafin, with a safer and more easily controlled regimen of low dose heparin.

Conclusions

Surgeons have been confronted with a plethora of studies on the subject of low dose heparin. Most recently, however, the American Heart Association's Council on thrombosis* has recommended the routine use of prophylactic low dose heparin, as a safe modality, in lowering the incidence of DVT and pulmonary embolus in general surgical patients over the age of 40. The safety in using low dose heparin in surgical patients is based on Kakkar's multicenter study.[16] In carefully analyzing the multicenter's data we find a bleeding complication rate of 16.6% with the use of low dose heparin. The 27% complication rate incurred with the use of low dose heparin in our own study would also seem to mitigate against its routine use. Until there is solid evidence that the mortality from pulmonary embolism is decreased with low dose heparin, its use should be limited to patients at highest risk. In treating these high risk patients with low dose heparin, however, one should be prepared to exchange a decrease incidence of DVT and pulmonary emboli for a higher bleeding and wound complication rate.

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